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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,830	12/05/2003	Florian Von Der Mulbe	2793-1-001PCT/CIP	8653

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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/729,830	VON DER MULBE ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 6-34* is/are pending in the application.

4a) Of the above claim(s) *17-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6-16 and 24-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/05, 1/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 1/27/2006, in which claims 2, 3 and 5 were canceled, claims 1, 4, 6-8, 11 and 24-26 were amended; and claims 29-34 were newly added. Currently, claims 1, 4 and 6-34 are pending. Applicants' arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow.

Any rejection of record in the previous office actions not addressed herein is withdrawn. New grounds of rejection are presented herein that were not necessitated by applicant's amendment of the claims since the office action mailed 8/25/2005. Therefore, this action is not final.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Applicant elected Group I (claims 1-16 and 24-28) with traverse in the reply filed on 7/1/2005. New claims 29-34 read on the invention of Group I.

Claims 17-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Claims 1, 4, 6-16 and 24-34 are under consideration.

Information Disclosure Statement

Receipt of an information disclosure statement, filed on 1/27/2006, is acknowledged. The signed and initialed PTO 1449 has been mailed with this action.

Receipt of an information disclosure statement, filed on 6/30/2005, is acknowledged. The signed and initialed PTO 1449 has been mailed with this action. A copy of the WO 01/04313 A1 reference has been provided since the prior Office action was mailed.

Oath/Declaration

The declaration filed 1/27/2006 has overcome the previous objection.

Specification – Computer Program Listing

The description portion of this application contains a computer program listing consisting of more than three hundred (300) lines. In accordance with 37 CFR 1.96(c), a computer program listing of more than three hundred lines must be submitted as a computer program listing appendix on compact disc conforming to the standards set forth in 37 CFR 1.96(c)(2) and must be appropriately referenced in the specification (see 37 CFR 1.77(b)(5)). Accordingly, applicant is required to cancel the computer program listing appearing in the specification on pages 30-67, file a computer program listing appendix on compact disc in compliance with 37 CFR 1.96(c) and insert an appropriate reference to the newly added computer program listing appendix on compact disc at the beginning of the specification. This is a new objection.

Claim Objections

Claim 25 is objected to because of the following informalities: the claim is written in a Markush-type format and should include the word "consisting" between the words "group" and

"of" to adhere to accepted terminology for this alternative expression. See MPEP 2173.05(h). Appropriate correction is required.

Response to Arguments - Claim Objections

The objection of claims 1-7, 11 and 19-28 has been withdrawn in view of Applicant's amendment to the claims.

Response to Arguments - Double Patenting

The rejection of claims 1, 2-5, 24 and 26 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 18 of copending Application No. 11/025,858 in view of Pavlakis has been withdrawn in view of Applicant's amendment to the claims. The previous rejection of claims 1, 2-5, 24 and 26 has been withdrawn.

Claim Rejections - 35 USC § 112

Claims 1, 4, 6-16 and 26-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a new rejection.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the

existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The claims are drawn to pharmaceutical compositions comprising an mRNA that encodes a polypeptide that is biologically active or antigenic. Thus, the claims encompass mRNA compositions for therapeutic purposes or vaccines.

Claim 1 and claims that depend therefrom are drawn to a pharmaceutical composition comprising at least one modified mRNA that encodes at least one polypeptide that is biologically active or antigenic, wherein the modified mRNA has the following characteristics: (i) an increase in Guanine/Cytosine (G/C) content relative to that of wild type mRNA encoding the polypeptide, (ii) a maximum G/C content, (iii) a sequence that encodes a polypeptide with a sequence identical to the wild type polypeptide, and (iv) a substitution wherein at least one codon recognized by a rare cellular tRNA is replaced by a codon recognized by an abundant cellular tRNA. Dependent claims 4 and 6-10 further limit the structure of the modified mRNA of claim 1. Dependent claims further limit the polypeptide encoded by the modified mRNA to a growth factor, tumor antigen, viral antigen, bacterial antigen or protozoal antigen (claim 11), a secreted polypeptide that is a viral, bacterial or protozoal antigen (claim 12), a polyepitope of a growth factor, tumor antigen, viral antigen, bacterial antigen or protozoal antigen (claim 13), a polyepitope of a tumor antigen, viral antigen, bacterial antigen or protozoal antigen (claim 14), a cytokine (claim 15), or a tumor antigen (claim 29). Claim 16 further limits the pharmaceutical composition comprising the modified mRNA to one that also comprises at least one cytokine.

Claim 26 is drawn to a pharmaceutical composition comprising an isolated modified

nucleic acid sequence comprising a nucleic acid sequence with the following characteristics: (i) a maximized G/C content, (ii) an increased frequency of codons recognized by abundant cellular tRNAs, (iii) a sequence that encodes a polypeptide with a sequence identical to the wild type polypeptide. Claims 27 and 28 further limit the pharmaceutical composition to one comprising at least one cytokine or adjuvant, respectively.

Claim 30 is drawn to a pharmaceutical composition comprising at least one modified mRNA that encodes at least one polypeptide that is biologically active or antigenic, wherein the mRNA has the following characteristics: (i) maximum G/C content, and (ii) a sequence that encodes a polypeptide with a sequence identical to the wild type polypeptide.

Claim 31 and claims that depend therefrom are drawn to a pharmaceutical composition comprising at least one modified mRNA that encodes at least one polypeptide, and a pharmaceutically compatible carrier and/or vehicle, wherein said modified mRNA has the following characteristics: (i) increase in G/C content relative to the wild type mRNA, and (ii) a sequence encoding a tumor antigen. Claim 32 further limits the increase in G/C content to at least 15% relative to that of the wild type mRNA encoding the tumor antigen. Claim 33 further limits the modified mRNA of claim 31 to one that has at least one codon of a wild type sequence recognized by a rare cellular tRNA replaced with a codon recognized by an abundant cellular tRNA, which recognizes the same amino acid as the rare cellular tRNA. Claim 34 is drawn to the pharmaceutical composition of claim 31, wherein the modified mRNA comprises a maximum G/C content and a maximum number of codons recognized by abundant tRNAs.

The nature of the subject matter is complex, because the nucleic acid must be delivered at a level sufficient to produce a therapeutic outcome (see the discussion below).

Breadth of the claims: The claims are broad in that they encompass pharmaceutical compositions comprising at least one modified mRNA encoding any polypeptide that has biological activity or is antigenic. Thus, the claims encompass pharmaceutical compositions for the treatment of any disease or for the vaccination against any infection or cancer. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification envisions the use of the modified mRNA for gene therapy and genetic vaccination for prophylactic and/or therapeutic treatments. The specification broadly envisions increasing or maximizing the G/C content of the mRNA to increase stability of the message and increasing the number of codons that are recognized by abundant cellular tRNAs rather than rare tRNAs to increase the translation efficiency of the message. With regard to gene therapy, the specification envisions the treatment of diseases with a modified mRNA encoding dystrophin, cystic fibrosis conductance transmembrane regulator (CFTR), enzymes that are lacking in metabolic disorders such as phenylketonuria, galactosaemia, homocystinuria, adenosine deaminiase deficiency, enzymes that are involved in the synthesis of neurotransmitter, insulin, growth hormones, etc. The specification thus envisions the use of the modified mRNA for the treatment of inherited Mendelian disorders, including inborn errors of metabolism, and complex traits such as neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease, diabetes, etc (e.g. paragraph [0050]). With regard to vaccination, the specification envisions the use of a modified mRNA for vaccination against virtually any infectious disease or cancer (e.g. paragraphs [0051]-[0052]).

While the specification and working examples teach how to make a modified mRNA that

meets the structural characteristics of the claimed invention, the specification does not teach how to use the pharmaceutical compositions for any therapy. No working examples that demonstrate a therapeutic outcome are provided.

State and predictability of the art: An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature, Vol. 389, pages 239-242, 1997; e.g. page 239, paragraph 1) and Palù et al (J. Biotechnol. Vol. 68, pages 1-13, 1999; e.g. Abstract) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al indicate that most approaches suffer from poor efficiency and transient expression of the gene (e.g. page 239, right column, paragraph 2). Likewise, Luo et al (Nature Biotechnology, Vol. 18, pages 33-37, 2000) indicate that non-viral synthetic delivery systems are very inefficient (e.g. Abstract; page 33, left column, paragraphs 1 and 2). Regarding viral methods for gene delivery *in vivo*, Verma et al, indicate that lentiviral, adenoviral and AAV vectors are capable of delivery genes, but there is a possibility for insertional mutagenesis or toxicity due to an inflammatory response (e.g. Table 2).

The area of the invention is unpredictable. As discussed above, the method of *in vivo* gene therapy is highly complex and unpredictable. Indeed, recent gene therapy protocols have demonstrated unpredictable outcomes resulting from an unexpected inflammatory reaction to an adenoviral vector in a patient and the insertional mutagenesis of a gene resulting in a leukemia-like condition in children being treated for severe combined immunodeficiency (Edelstein et al,

J. Gene Med. Vol. 6, pages 597-602, 2004; e.g. page 599, The hopes and the setbacks). The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect.

The use of RNA for vaccinations is unpredictable in that the process depends upon cell-specific and tissue-specific efficient transfer of the nucleic acid (e.g. specification, paragraph [0009]). Furthermore, the success of nucleic acid vaccination is unpredictable with regard to obtaining a prophylactic or therapeutic effect (Dunham, S.P. Research in Veterinary Science, Vol. 73, pages 9-16, 2002; e.g. pages 13-14). Dunham teaches that each vaccine in development must be optimized with regard to route and dose of inoculation for each target species due to the unpredictable nature of nucleic acid vaccines and the suboptimal delivery of the nucleic acid vaccine in many situations (e.g. page 13, right column, last paragraph; Table 1). In fact, the efficacy of genetic vaccines in many systems has not proven satisfactory, which has led some to conclude that genetic vaccines are not a viable alternative to conventional vaccines and may not be sufficiently immunogenic for the therapeutic vaccination of patients with infectious diseases or cancer in clinical trials (Lietner et al, Vol. 18, pages 765-777, 2000; e.g. Abstract, and page 766, right column).

Amount of experimentation necessary: The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to make and use the claimed methods commensurate in scope with the claims. With any modified mRNA one would have to determine how to deliver the given mRNA the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. Since neither the prior art nor the

specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 1, 4, 6-16 and 26-34 are not considered to be enabled by the instant specification.

Response to Arguments - 35 USC § 112

The rejection of claims 1, 6-16, 24 and 25 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of Applicant's amendment to the claims in the reply filed 1/27/2006. The previous rejection of claims 1, 6-16, 24 and 25 has been withdrawn.

The rejection of claims 1, 6 and 7 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, has been withdrawn in view of Applicant's amendment to the claims in the reply filed 1/27/2006. The previous rejection of claims 1, 6 and 7 has been withdrawn.

The rejection of claims 1 and 8 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, has been withdrawn in view of Applicant's amendment to the claims in the reply filed 1/27/2006. The previous rejection of claims 1 and 8 has been withdrawn.

Claim Rejections - 35 USC § 102

Claim 24 is rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al (WO 99/20774, cited in a prior action; see the entire reference). This ground of rejection has been altered relative to the rejection presented in the Office action mailed 8/25/2005.

Claim 24 is drawn to an isolated modified nucleic acid sequence comprising a nucleic acid sequence with the following characteristics: (i) a maximized G/C content, (ii) an increased frequency of codons recognized by abundant cellular tRNAs, (iii) a sequence that encodes a polypeptide with a sequence identical to the wild type polypeptide.

Chen et al teach a vaccine comprising a modified nucleic acid sequence with overall increased GC content, and increased frequency of codons recognized by abundant cellular tRNAs (e.g. page 3). Further, Chen et al teach a modified MSP-1 nucleic acid, wherein all rare codons are replaced with preferred codons, and all mRNA instability motifs are eliminated (e.g. page 3). Further, Chen et al teach that the replaced codons code for the same amino acids as the wild type codon (e.g. page 3). Chen et al exemplify the creation of a modified MSP-1 gene, which has codons changed to mammary tissue specific codon usage and a maximum G/C content of 49.7% relative to a G/C content of 76% for the wild type sequence (e.g. pages 9-10).

Claim 24 reads on the teachings of Chen et al, because there is no structural difference between the product produced by the method steps recited in instant claim 24 and the sequence taught by Chen et al.

Response to Arguments - 35 USC § 102

Applicant's arguments, see pages 14-15, filed 1/27/2006, with respect to the rejection of claims 1, 3, 6, 11-15, 24 and 26 under 35 U.S.C. 102(b) as being anticipated by Pavlakis et al are moot in view of the new ground(s) of rejection under 35 U.S.C. § 112, 1st paragraph.

Applicant's arguments, see pages 15-16, filed 1/27/2006, with respect to the rejection of claims 1, 8, 9 and 11-16 under 35 U.S.C. 102(b) as being anticipated by Felgner are moot in view of the new ground(s) of rejection under 35 U.S.C. § 112, 1st paragraph.

With respect to the rejection of claim 24 under 35 U.S.C. 102(b) as being anticipated by Chen et al, Applicant's arguments filed 1/27/2006 have been fully considered but they are not persuasive.

The response asserts that Chen et al does not teach increasing GC content, because decreasing the overall AT content will not result in maximum GC content, especially within the context of the other recited features of claim 24. This is not found persuasive because if overall AT content is decreased, the only other nucleotides available to replace A or T are G and C. Thus, the sequence will necessarily have an overall increase in GC content. Further, Chen et al specifically increase the content of GC within the context of replacing codons to more abundant cellular tRNAs found in mammary cells. Thus, Chen et al are providing the maximum GC content within the context of replacing all rare codons, as required by claim 24.

The response asserts that Chen et al teach the modification of MSP-1 of the malaria parasite, and thus the teachings of are directed to a particular gene and are not broadly directed to a modified nucleic acid sequence. This is not found persuasive, because a single prior art species anticipates a claimed genus. "A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus." The species in that case will anticipate the genus. *In re Slayter*, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); *In re Gosteli*, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989). See MPEP § 2131.02.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Response to Arguments - 35 USC § 103

Applicant's arguments, see pages 17-18, filed 1/27/2006, with respect to the rejection(s) of claim(s) 1-9, 11-16, 24 and 26-28 under 35 U.S.C. 103(a) as being unpatentable over Chen et al in view of Felgner et al are moot in view of the new ground(s) of rejection under 35 U.S.C. § 112, 1st paragraph.

Applicant's arguments, see pages 18-20, filed 1/27/2006, with respect to the rejection of claims 1, 3, 6, 9-15, 24 and 26 under 35 U.S.C. 103(a) as being unpatentable over Pavlakis et al in view of Ueda et al are moot in view of the new ground(s) of rejection under 35 U.S.C. § 112, 1st paragraph.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR, http://pair-direct.uspto.gov) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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